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Quantitative magnetic resonance imaging of the corpus callosum in childhood onset schizophrenia

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Abstract

Corpus callosum size has been found to be abnormal in adult schizophrenia, and other studies have implicated abnormal interhemispheric communication in this disorder. To assess continuity with brain abnormalities in the later onset disorder and to further localize brain maldevelopment, this structure was examined in a unique sample of childhood onset schizophrenics. Anatomic brain magnetic resonance imaging scans were acquired for 25 patients (mean age 13.9 ± 2.1) who had onset of schizophrenia by age 12 (mean age at onset 9.9 ± 1.9) and 55 normal children. The midsagittal area of the corpus callosum was divided into seven sections. With no adjustment for brain volume, no diagnostic differences were observed. After adjustment for the smaller cerebral volume of the schizophrenics, larger total, anterior and posterior corpus callosum areas emerged for the schizophrenics. These findings provide further evidence for continuity between childhood onset and later onset schizophrenia and support other studies showing white matter sparing in the context of decreased cortical volume.

Keywords: Neurodevelopment; White matter; Gray matter; Midsagittal

1. Introduction

Study of children and adolescents with very early onset schizophrenia may offer unique opportunities to test neurodevelopmental hypotheses of the etiology of schizophrenia. This population, although clinically similar to later onset schizophrenics (Gordon et al., 1994; Green et al., 1992; Russell, 1994; Spencer and Campbell, 1994), exhibits greater premorbid impairments (Alaghband-Rad et al., 1995; Russell, 1994) and a more chronic course of illness (Gordon et al., 1994), possibly due to a more severe genetic and/or environmentally determined neurodevelopmental insult.

The first quantitative brain magnetic resonance

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imaging (MRI) study of childhood onset schizophrenics has demonstrated significantly smaller total cerebral volume and midsaggital thalamic area, larger caudate, putamen, and globus pallidus volumes; a trend toward larger lateral ventricular and superior temporal gyrus volumes; but no diagnostic differences in temporal lobe, medial temporal lobe, or frontal volumes (Frazier et al., 1996; Jacobsen et al., 1996b). These findings generally support other neurobiologic studies indicating continuity with later onset schizophrenia (Gordon et al., 1994; Spencer and Campbell, 1994; Jacobsen et al., 1996a; Jacobsen et al., 1997). Examination of effect sizes has indicated a significantly larger effect size for decreased cerebral volume than that reported for later onset schizophrenia (Alaghband-Rad et al., unpublished results).

Abnormal interhemispheric communication has been demonstrated in a number of neuropsychologic and neurophysiologic studies of adult schizophrenics (Coger and Serafetinides, 1990; David, 1994) and in children at risk for schizophrenia (Fish, 1984; Hallett et al., 1986). The greater prevalence of partial corpus callosum agenesis in schizophrenics relative to controls (Swayze et al., 1990) suggests that abnormal development of this principal interhemispheric commissure may contribute to schizophrenic pathology, including aberrant interhemispheric communication.

Despite evidence of functional and neurodevelopmental corpus callosum abnormalities in schizophrenia, morphological studies of the corpus callosum in adult onset schizophrenia have been inconclusive. While an early postmortem study found increased callosal thickness in schizophrenics (Bigelow et al., 1983), a subsequent postmortem study (Brown et al., 1986) failed to replicate this finding. Though a recent meta-analysis of brain magnetic resonance imaging (MRI) studies of the corpus callosum suggests that this structure tends to be smaller in schizophrenics (Woodruff et al., 1995), individual MRI studies examining total corpus callosum area have found larger (Nasrallah et al., 1986), smaller (Woodruff et al., 1993; Rossi et al., 1990; Stratta et al., 1989), and unremarkable (Hauser et al., 1989; Uematsu and Kaiya, 1988; Mathew et al., 1985; Casanova et al., 1990; Raine et al., 1990; Günther et al., 1991; Kelsoe et al., 1988; Machiyama et al., 1987; Smith et al., 1987) callosal size in schizophrenic relative to control subjects. These various findings held after adjustment for brain size (Nasrallah et al., 1986; Woodruff et al., 1993; Uematsu and Kaiya, 1988; Mathew et al., 1985; Günther et al., 1991; Raine et al., 1990; Kelsoe et al., 1988; Stratta et al., 1989; Smith et al., 1987) and exhibited no clear relationship to the age of the schizophrenic group. Gender effects on corpus callosum morphology in schizophrenia have also been inconsistent (Nasrallah et al., 1986; Hoff et al., 1994; Raine et al., 1990). Some of these inconsistent findings may reflect the technical challenge of obtaining a true midsaggital slice for measurement of corpus callosum area (Coppola et al., 1995).

Comparison of subdivisions of the corpus callosum may reveal more subtle morphologic abnormalities in schizophrenia. Three studies finding no difference between schizophrenics and controls divided the corpus callosum into three to five subdivisions and did not adjust for brain size (Hauser et al., 1989; Casanova et al., 1990; Machiyama et al., 1987). One study dividing the callosum into quarters and, adjusting for brain size, found midanterior and midposterior quarters to besmaller in schizophrenics (Woodruff et al., 1993). Finally, one study dividing the callosum into thirds and adjusting for brain size found the anterior third to be larger in schizophrenics (Uematsu and Kaiya, 1988).

In the present study, corpus callosum morphology was examined in a childhood onset sample with a potentially more severe neurodevelopmental abnormality producing early and more malignant disease. Total area of the corpus callosum as well as the areas of seven callosal subdivisions, corresponding to specific brain regions (Witelson, 1989), were examined. This methodology, derived from postmortem studies, permits more precise characterization of regional abnormalities of the callosum (Witelson, 1989). Accuracy of location of the midsaggital slice was confirmed using landmarks in the axial plane. Evidence for continuity of callosal abnormalities

between early and later onset schizophrenia was assessed along with evidence for greater severity of callosal abnormalities, possibly reflecting a more severe neurodevelopmental lesion.

Increasing evidence indicates both regional (Zipursky et al., 1994; Schlaepfer et al., 1994) and global gray matter deficits in schizophrenia (Zipursky et al., 1992) in the context of white matter sparing. These in vivo observations may reflect increased cortical neuronal density as opposed to neuronal loss (Selemon et al., 1995). Hypothesizing that the decreased total cerebral volume of childhood onset schizophrenics is due primarily to reduced gray matter, we predicted that the corpus callosum of these patients would be spared and thus as a whole would be relatively larger in childhood onset schizophrenics after adjustment for their significantly smaller total cerebral volume.

2. Methods

2.1. Subjects

Children and adolescents were recruited nationally for an ongoing study of childhood onset schizophrenia involving a controlled clozapine treatment trial (Frazier et al., 1994; Gordon et al., 1994). Inclusion criteria were: DSM-III-R (American Psychiatric Association, 1987) diagnosis of schizophrenia, with onset of psychotic symptoms by age 12, premorbid IQ of 70 or above, absence of medical or neurologic disease, and history of poor response to and/or inability to tolerate treatment with at least two different neuroleptics. Diagnosis was determined using previous records, and clinical and structured interviews of the children and parents based on portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (Puig-Antich et al., 1980) and of the Diagnostic Interview for Children and Adolescents Revised (DICA-R) (Reich and Welner, 1988).

All 25 schizophrenic subjects (12 girls, 13 boys), ages 9 to 18 (mean $\pm$ S.D.,13.9 $\pm$ 2.1), had evidence of pubertal change (Tanner score of 3.7 $\pm$ 1.2, range 1.5–5). The mean age at the time of onset of psychotic symptoms was 9.9 $\pm$ 1.9 years (range 5–12 years), and the group as a whole had undergone substantial treatment, both in terms of duration of neuroleptic therapy (24.3 $\pm$ 17.2 months) and previous hospitalizations (7.9 $\pm$ 12.9 months). There was no history of substance or alcohol abuse or electroconvulsive therapy in the sample. Mean Vocabulary and Block Design subtest scores from the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974) were 6.0 $\pm$ 3.7 and 6.8 $\pm$ 3.7, respectively. Six schizophrenic subjects were unable to complete the Vocabulary subtest and four were unable to complete the Block Design subtest of the WISC-R. MRI scans were obtained while subjects were on admission medications.

Fifty-five normal children and adolescents, selected to be similar to the patients in age (14.1 $\pm$ 2.0), sex (31 boys, 24 girls), and handedness, were recruited through local advertisements. Medical, neurologic, and psychiatric illnesses and learning disabilities were exclusionary. Conners Preliminary Parent Report and the Achenbach Child Behavior Checklist (Achenbach and Edelbrock, 1983) were completed by parents, and Conners Teacher Preliminary School Report and Conners Teacher Questionnaire (Goyette et al., 1978; Werry et al., 1975) were obtained from teachers. Physical and neurologic exam of the child, and structured interview of child and parent using the DICA-R were performed. Any history of psychiatric illness in a first degree relative was also exclusionary. Mean vocabulary and block design WISC-R subtest scores for the normal controls were 13.0 $\pm$ 2.6 and 13.5 $\pm$ 3.0, respectively.

Handedness was determined using the 12 handedness items from the Physical and Neurological Examination for Subtle Signs (PANESS) (Denckla, 1985). Subjects performing 10 or more handedness items (83%) with one hand were classified as right or left handed; all others were classified as mixed. Characteristics of schizophrenic and healthy control groups are summarized in Table 1.

Parents of all subjects provided written informed consent, and subjects provided assent for participation in the study. This study was approved by the NIMH Institutional Review Board.

Table 1
Characteristics of childhood onset schizophrenics and healthy controls

	Schizophrenics $N = 25$ Mean ± S.D.	Healthy controls $N = 55$ Mean ± S.D.
Age (years)	13.9 ± 2.1	14.1 ± 2.0
Gender (M/F)	13/12	31/24
Height[a] (cm)	159.3 ± 12.4	164.1 ± 14.3
Weight (kg)	59.6 ± 18.0	54.9 ± 13.1
Tanner stage	3.7 ± 1.2	3.4 ± 1.4
Handedness (R/L/M)[b]	18/5/2	47/7/1
Vocabulary[c]	6.0 ± 3.7	13.0 ± 2.6
Block design[d]	6.8 ± 3.7	13.5 ± 3.0
Age at onset (years)	9.9 ± 1.9	—
Previous neuroleptic exposure (months)	24.3 ± 17.2	
Previous hospitalization (months)	7.8 ± 12.9	—

[a] Height for $n = 24$ schizophrenics and $n = 54$ controls.
[b] R = right, L = left, M = mixed.
[c] Vocabulary subtest score on 19 schizophrenics, 54 controls, $t = 8.93$, $P < 0.0001$.
[d] Block design subtest score on 21 schizophrenics, 54 controls, $t = 8.10$, $P < 0.0001$.

2.2. MRI image acquisition

All subjects were scanned on a GE 1.5 Tesla Signa magnetic resonance scanner. As described elsewhere (Giedd et al., 1996a), head position was stabilized with the use of foam padding. Head alignment was standardized by placing a vitamin E capsule in the meatus of each ear, taping one capsule to the left inferior orbital ridge, and then insuring that all three capsules were visible in the same axial reference plane. Subjects were scanned in the evening to promote their falling asleep. Sedation was used with 14 of the schizophrenic subjects.

Mostly T1 weighted images with contiguous sagittal and axial slice thickness of 1.5 mm and coronal slice thickness of 2.0 mm were acquired using a three-dimensional spoiled gradient recalled echo sequence in the steady state (TE = 5 ms, TR = 24 ms, flip angle = 45°, acquisition matrix = 192 × 256, NEX = 1, and FOV = 24 cm).

2.3. Image analysis

All scans were read by a clinical neuroradiologist who found no abnormalities in the control scans. One patient's scan showed enlargement of the left lateral ventricle, and another demonstrated a focal area of increased signal in the left frontal white matter. These images were retained in the data set.

MRI data were analyzed using image analysis software developed at the NIH (Rasband, 1993). The midsagittal plane image was generated from the three-dimensional axial data set by drawing a line to bisect the cerebral hemispheres in the axial slice containing the anterior and posterior commissures. An image in the sagittal plane perpendicular to the axial plane and encompassing the operator-selected midline was then constructed. Midsagittal orientation was confirmed by patency of the cerebral aqueduct and distinctness of the thalamus.

Within the midsagittal slice, an elliptical region of interest encompassing the corpus callosum was drawn, and, within this region, a supervised thresholding technique was used to determine the X-Y coordinates of the corpus callosum perimeter. These measures were performed by a single rater (ACV) who was blind to subject diagnosis, age, and gender. Twenty randomly selected scans were measured twice, yielding an average in-

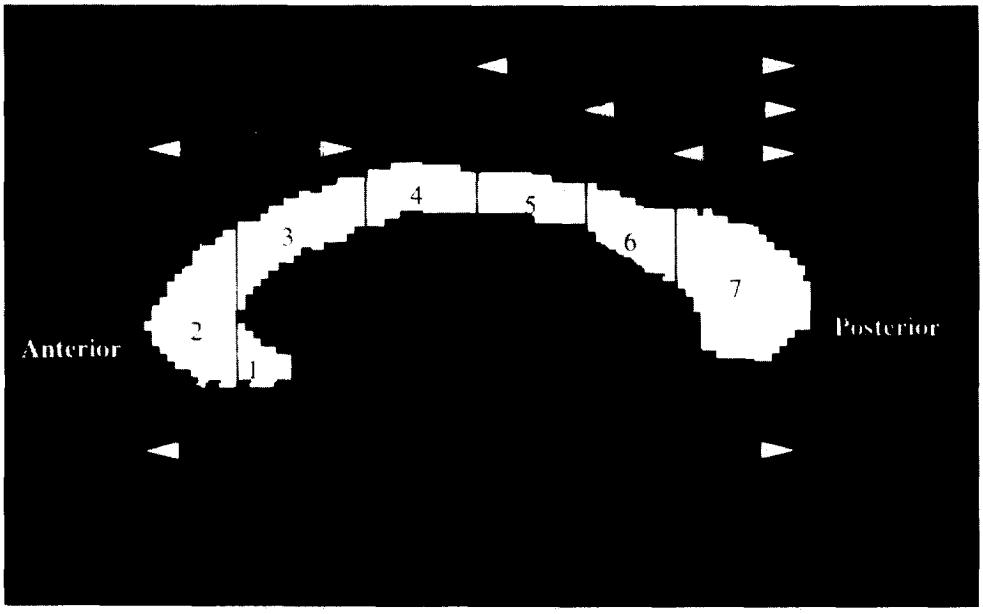
trarater reliability (intraclass correlation coefficient, ICC) of 0.92 for the seven subdivisions of the corpus callosum.

After Witelson (1989), the area of the midsagittal corpus callosum was divided into seven subdivisions, as shown in Fig. 1. Areas of the seven subdivisions were determined after transferring the X-Y coordinates of the corpus callosum perimeter to a Unix workstation. A line was then drawn from the most anterior point (ACC) to the most posterior point (PCC) of the corpus callosum. To correct for differences in spatial orientation of the corpora callosa, the outline of each corpus callosum was then rotated until the ACC-PCC line became horizontal. Areas of the seven subdivisions were determined using a computerized algorithm which drew 100 equally spaced radial lines from the mid-point of the ACC-PCC line to the dorsal and ventral boundaries spanning from the tip of the rostrum to the end of the splenium. Corpus callosum area between two adjacent lines was computed using the distances to the dorsal and ventral boundaries and the angle between them (Rajapakse et al., 1996). This method of area calculation more closely models the natural, smooth boundary of the corpus callosum than pixel-counting methods, where boundaries of the corpus callosum follow the edges of quadratic pixels and thus are not smooth (Rajapakse et al., 1996).

As previously described (Giedd et al., 1996a; Snell et al., 1995), total cerebral volume was quantified using an image analysis program which supplements MRI signal intensity characteristics with a template based upon a priori information about expected brain surface shape and location. Further details of this program are provided elsewhere (Snell et al., 1995; Giedd et al., 1996c).

2.4. Statistical analysis

Group differences on demographic variables and total cerebral volume were assessed with chi-square analyses and *t*-tests for independent



Adapted from Witelson (1989) : 1=Rostrum, 2=Genu, 3=Rostral Body, 4=Anterior Midbody, 5=Posterior Midbody, 6=Isthmus, 7=Splenium

Fig. 1. Schematic of midsagittal corpus callosum subdivisions.

samples. Medication effects were examined using Pearson's correlation coefficients. Callosal morphology was examined across subdivisions using repeated measures analysis of variance and covariance with diagnosis and gender as between subjects factors, callosal subdivision as a within subject factor, and total cerebral volume as a covariate. The importance of adjusting for total cerebral volume has been underscored by the recent observation that cranial size significantly predicts both total and regional corpus callosum size (Parashos et al., 1995). Regression slopes between corpus callosum subdivision areas and age were also examined. All tests were two- tailed and P values less than 0.05 were considered statistically significant. Analyses were conducted using SAS (SAS Institute Inc., 1989).

3. Results

There were no significant differences between patients and controls in age, height, weight, Tanner stage, gender, or handedness. Children with schizophrenia had significantly lower mean WISC-R vocabulary and block design subtest scores and 9.1% smaller total cerebral volume ($t = 3.59$, df = 78, $P < 0.001$). Comparing male schizophrenics with male controls, the difference in total cerebral volume achieved only a trend ($t = 1.81$, df = 42, $P = 0.08$), whereas this difference between female schizophrenics and female controls was highly significant ($t = 5.0$, df = 34, $P < 0.0001$).

3.1. Corpus callosum morphology

Mean unadjusted areas for the total corpus callosum and the seven corpus callosum subdivisions for schizophrenics and normal controls are shown in Table 2, along with the same measures adjusted for total cerebral volume.

There was a significant gender difference for the total corpus callosum area ($F = 4.73$, df = 2,77, $P < 0.05$), with the callosum being larger in males. This effect of gender was significant specifically at the rostral body ($F = 6.87$, df = 1,76, $P < 0.05$), anterior midbody ($F = 5.18$, df = 1,76, $P < 0.05$), posterior midbody ($F = 4.21$, df = 1,76, $P < 0.05$), and the isthmus ($F = 6.53$, df = 1,76, $P < 0.05$), with males being larger than females in all cases. There were no significant diagnostic differences, but diagnosis by gender interactions for the posterior midbody ($F = 3.54$, df = 1,76, $P = 0.06$) and the isthmus ($F = 3.13$, df = 1,76, $P = 0.08$) approached significance. Inspection of unadjusted means suggested that these structures were larger for male schizophrenics than for controls and female schizophrenics.

After adjusting for total cerebral volume, the total corpus callosum area wassignificantly larger

Table 2
Total and subdivision areas of the corpus callosum for childhood onset schizophenics ($N = 25$) and healthy controls ($N = 55$)[a]

	Unadjusted means ± S.D.				Adjusted means[b]			
	Males		Females		Males		Females	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Total	703.2 ± 126.2	643.3 ± 84.9	602.4 ± 71.5	624.9 ± 78.4	699.4	613.1	661.9	636.3
Rostrum	85.5 ± 28.6	69.5 ± 25.3	73.0 ± 18.2	67.6 ± 24.2	85.2	66.6	78.8	68.7
Genu	64.4 ± 23.9	57.4 ± 14.8	52.9 ± 13.2	61.5 ± 31.1	63.8	52.9	61.8	63.2
Rostral body	162.9 ± 32.3	147.7 ± 22.5	136.6 ± 23.6	142.1 ± 24.9	161.8	138.7	154.2	145.5
Anterior midbody	77.9 ± 14.1	77.0 ± 10.5	70.2 ± 11.7	72.7 ± 8.6	77.5	74.0	75.9	73.8
Posterior midbody	78.2 ± 18.7	70.2 ± 10.3	66.6 ± 12.0	69.7 ± 10.0	77.9	68.4	70.0	70.4
Isthmus	76.2 ± 25.1	64.4 ± 14.2	60.1 ± 10.7	61.4 ± 11.6	75.8	61.5	65.8	62.5
Splenium	171.6 ± 41.0	172.0 ± 31.4	160.1 ± 22.0	166.4 ± 30.2	170.8	165.8	172.3	168.8

[a]All areas in mm^2.
[b]Adjusted for total cerebral volume.

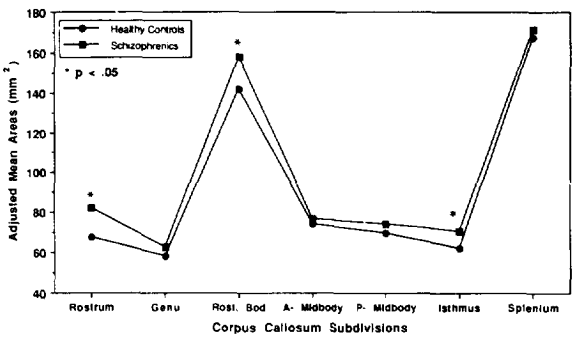


Fig. 2. Mean corpus callosum subdivision areas adjusted for total brain volume for childhood onset schizophrenics ($N = 25$) and healthy controls ($N = 55$).

for the schizophrenics ($F = 7.56$, df = 2,76, $P < 0.01$). All gender differences were lost. The diagnostic differences were significant at the rostrum ($F = 4.79$, df = 1,75, $P < 0.05$), the rostral body ($F = 6.84$, df = 1,75, $P < 0.05$), and the isthmus ($F = 4.84$, df = 1,75, $P < 0.05$), with schizophrenics having larger areas for each of these subdivisions than controls. Diagnosis by gender interactions for the posterior midbody ($F = 2.78$, df = 1,75, $P = 0.10$) and the isthmus ($F = 2.27$, df = 1,75, $P = 0.14$) were considerably weaker. Neither analysis of variance nor analysis of covariance revealed significant diagnosis by corpus callosum subdivision interactions. Corpus callosum subdivision areas adjusted for total cerebral volume for schizophrenics and healthy controls are shown in Fig. 2.

While the area of the splenium increased significantly with age within the control group (slope = 2.4 mm^2/year, $P < 0.05$), no other corpus callosum subdivision within this group changed with age. The schizophrenic group showed no significant age-related changes in corpus callosum morphology.

Within the schizophrenic group, no significant relationships were found between absolute subdivision area and lifetime antipsychotic exposure (summed doses in chlorpromazine equivalents × length of trials) or total number of months of neuroleptic exposure (all P values > 0.13), suggesting that the relatively larger size of corpus callosum subdivisions in schizophrenics is not associated with drug treatment.

4. Discussion

As predicted, total corpus callosum area was relatively larger in childhood onset schizophrenics. This finding is consistent with one previous study of a sample of chronic adult schizophrenics conducted by Nasrallah et al. (1986) and supports continuity between childhood and later onset forms of this disorder. Effect sizes for total callosum area in the present study and in the study by Nasrallah et al. were compared using z scores, and did not differ significantly, thus failing to support a more severe neurodevelopmental deviation of the corpus callosum for our childhood onset sample.

The observation of a relatively larger corpus callosum in childhood onset schizophrenia is also consistent with a recent postmortem study by Selemon et al. (1995) indicating that the schizophrenic disease process is associated with a reduction in neuropil throughout the cortex leading to increased neuronal density, particularly in cortical layer V, without actual neuronal loss. Given this reduction in cortical volume due to denser packing of neuronal cell bodies, the corpus callosum, which consists of fiber tracts from these neurons, would be expected to be relatively larger in schizophrenics after correction for total cerebral volume. Recent observation of decreased gray matter with sparing of cortical white matter in a sample of adult schizophrenics, some of whom had disease onset in childhood and early adolescence (Lim et al., 1996), is also consistent with our corpus callosum findings and with the findings of Selemon et al. (1995). Together, these observations suggest a pattern of gray matter abnormalities with relative sparing of white matter in schizophrenia. The demonstration that first trimester irradiation of fetal monkeys results in increased cortical neuronal density (Algan et al., 1992) indicates that this pattern of abnormalities is consistent with a disturbance of early neurodevelopment. The observation of the same pattern

of gray matter reduction with white matter sparing in patients with congenital rubella and schizophrenia-like symptoms as is found in schizophrenic patients indicates that a viral disturbance of early neurodevelopment can produce this pattern of brain dysmorphology (Lim et al., 1995).

Our inability to examine relationships between callosal subdivisions and the volumes of regions of origin of axons contained in each subdivision limits what can be interpreted from the subdivision analysis. Callosal subdivisions that were relatively enlarged in childhood onset schizophrenics included the isthmus, which tends to contain axons from the superior temporal and posterior parietal regions, and two anterior subdivisions, the rostrum and rostral body, which tend to contain fibers originating in frontal cortex (Witelson, 1989). These observations are consistent with one study which demonstrated relative enlargement of the anterior third of the corpus callosum in adult schizophrenics (Uematsu and Kaiya, 1988) and may suggest particular sparing of white matter originating from these brain regions in schizophrenia. However, a more definitive examination of gray versus white matter deficits in this population must await gray/white segmentation.

The observation of significant age-related increases in the splenium for normals is consistent with findings from a larger study of corpus callosum development in children, which demonstrated greater age-related changes in posterior than anterior callosal regions (Giedd et al., 1996b). The lack of significant age-related changes in the schizophrenic group may be due to the small size and narrow age range of the schizophrenic group.

Replication of these findings with larger numbers of subjects, permitting clarification of gender effects, is needed. While the inclusion criterion of neuroleptic non-response may have independently selected for greater brain abnormalities (Crow, 1985), phenomenologic similarities between this sample and other samples of childhood onset schizophrenics (Green et al., 1992; Russell, 1994; Spencer and Campbell, 1994) support the relevance of these findings to childhood onset schizophrenia in general. Furthermore, the lack of evidence of more severe brain abnormalities in this sample of childhood onset schizophrenics relative to adult schizophrenics (Frazier et al., 1996) also argues against this selection bias.

Ongoing analyses of brain morphology in this sample, particularly gray/white segmentation, may clarify location of brain abnormalities in schizophrenia, and the maturational events triggering early disease onset.

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